CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Correspondence

Pharmacia&Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (269) 833-4000

March 25, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 21-106

SOMAVERT®
(pegvisomant for injection)

Amendment to Pending NDA

Dear Sir/Madam:

Pharmacia and Upjohn (P & U) is submitting its 25 March 2003 version of Patients Package Insert (PPI) with both 9-digit and 6-digit identifier numbers and today's (25 March 2003) date on Header. We are providing the Agency both an electronic (CD-ROM) as well as a hard copy of the PPI. In addition, we are providing WORD and pdf versions via E-mail.

The CD-ROM contains the following files and directory structure:

Main Directory – N21106

- Cover Letter (cover.pdf)
- 356h Form (356h.pdf)
- Table of Contents (ndatoc.pdf)

Subdirectory – Labeling

- Patient Package Insert (Proposed PPI.doc) *for editing*
- Patient Package Insert (proposed PPI.pdf)
- Table of Contents (labeltoc.pdf)

Please direct any questions regarding this amendment to the undersigned by telephone at (269) 833 8095 or by facsimile at (269) 833 8237. Mail correspondence may be directed to Mail Stop 0200-298-106 at the address provided in our letterhead above.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Satish Tripathi, PhD, RAC
Director, Global Regulatory Affairs

ST:SEH
Attachments

cc: Ms. Enid Galliers, Supervisory Project Manager
Division of Metabolic and Endocrine Drug Products (HFD-510)

8 page(s) of revised draft labeling has been redacted from this portion of the review.

DUPLICATE

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

March 24, 2003

RECEIVED
MAR 25 2003
CDR/CDER

RECEIVED
MAR 26 2003
FDR/CDER

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

BL
ORIG AMENDMENT

RE: NDA 21-106

SOMAVERT®
(pegvisomant for injection)

ORIG AMENDMENT

Amendment to Pending NDA

Dear Sir/Madam:

Pharmacia and Upjohn (P & U) would like to thank FDA for its agreement to 19 March 2003 versions of Package Insert and Patients Package Insert. We are providing the Agency electronic (CD-ROM) version and hard copies of the following items:

1. Package Insert (Black and White) with all the changes made as agreed upon to date;

2. Patient Package Insert (Black and White) with all the changes made as agreed upon to date;

3. Diluent Label (Color Print);

4. Label for Drug Product vials and Carton (Color Print)

The CD-ROM contains the following files and directory structure:

Main Directory – N21106

- Cover Letter (cover.pdf)
- 356h Form (356h.pdf)
- Table of Contents (ndatoc.pdf)

Subdirectory – Labeling

- Package Insert (proposed PI.pdf)
- Package Insert (Proposed PI.doc) *for editing*
- Patient Package Insert (Proposed PPI.doc) *for editing*
- Patient Package Insert (proposed PPI.pdf)
- Diluent Label (Diluent Label.pdf)
- Proposed Product Labeling (Label 10 mg.pdf)
- Proposed Product Labeling (Label 15 mg.pdf)
- Proposed Product Labeling (Label 20 mg.pdf)

- Carton Label (Carton 10 mg.pdf)
- Carton Label (Carton 15 mg.pdf)
- Carton Label (Carton 20 mg.pdf)

The enclosed CD-ROM has been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.00 and found to be virus free.

Please direct any questions regarding this amendment to the undersigned by telephone at (269) 833-8095 or by facsimile at (269) 833-8237. Mail correspondence may be directed to Mail Stop 0200-298-113 at the address provided in our letterhead above.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Satish Tripathi, PhD, RAC
Director, Global Regulatory Affairs

ST:SEH
Attachment

cc: Ms. Enid Galliers, Supervisory Project Manager
Division of Metabolic and Endocrine Drug Products (HFD-510)

33 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

10.7.02

Pharmacia and Upjohn
Attention: Satish Tripathi, PhD, RAC
Director, Global Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Dr. Tripathi:

We acknowledge receipt on September 30, 2002, of your September 27, 2002, resubmission to your new drug application (NDA) for Somavert (pegvisomant) for injection.

This resubmission contains additional information regarding facility inspection readiness in response to our June 26, 2001 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 31, 2003.

If you have any questions, call me at (301) 827-6370.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Monika Johnson
10/7/02 11:00:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

9.27-02

Pharmacia & Upjohn
Attention: Satish Tripathi, PhD, RAC
Director, Global Regulatory Affairs
7000 Portage Road
Unit 0638-298-106
Kalamazoo, MI 49001

Dear Dr. Tripathi:

We acknowledge receipt on August 30, 2002, of your August 29, 2002, submission to your new drug application (NDA) for Somavert (pegvisomant for injection).

This submission labeled as a "Complete Response to Approvable Letter of 26 June 2001," contained responses to the Chemistry, Manufacturing and Controls, Pharmacology/Toxicology, Administrative and Labeling items. However, we do not consider this a complete response to our action letter because all of the manufacturing facilities were not ready for inspection on the date of your submission.

We received a letter dated September 12, 2002, indicating that the ——— ——— facilities will be ready for inspection "during the week of October 7, 2002". In order to be considered a complete response our June 26, 2001 approvable letter and restart the review clock, you will need to submit a letter for delivery to the Agency on the date that the sites are ready for inspection.

If you have any questions, call Monika Johnson, PharmD, Regulatory Project Manager at (301) 827-6370.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
9/27/02 10:58:16 AM

09-28-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

Pharmacia & Upjohn Co.
Attention: Leslie A. Franks
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Franks:

We acknowledge receipt on August 30, 2001, of your August 17, 2001, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: B2036-PEG (pegvisomant)

NDA Number: 21-106

Name of New Applicant: Pharmacia & Upjohn Co.

Name of Previous Applicant: Sensus Drug Development Co.

Date Transfer Effective: August 16, 2001

Your correspondence provided the information necessary to effect this change and we have revised our records to indicate Pharmacia & Upjohn Co. as the sponsor of record for this application. Please note that all changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, require an approved supplement before implementation.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Sensus Drug Development Co.
Attention: Robert Davis, M.D.
98 San Jacinto, Suite 430
Austin, TX 78701

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Enid Galliers
9/28/01 12:02:47 PM

07-13-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-106

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Dear Dr. Davis:

We received the July 3, 2001, correspondence on July 5, 2001, from Pharmacia Corporation requesting a meeting to discuss the chemistry deficiencies outlined in our June 26, 2001, approvable letter. We note that you are the sponsor of record; thus we are addressing this response to you.

We considered your request and concluded the meeting is unnecessary. The specific questions you propose essentially request an opinion on the approvability of your planned resubmission. However, the Division cannot comment on the approvability of an application prior to its official submission and the completion of our review of it. Two of your listed questions were appropriate and will be answered during a teleconference on July 18, 2001.

If you disagree with our decision, you may discuss the matter with Crystal King, P.D., M.G.A., Regulatory Project Manager, at 301-827-6423. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
7/13/01 07:18:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

DISCIPLINE REVIEW LETTER

5/17/01

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
98 San Jacinto Boulevard
Austin, TX 78701

Dear Dr. Davis:

Please refer to your December 22, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Somavert (pegvisomant) for injection.

We also refer to your submissions dated February 22 and 27, April 17, 18, 24, and 25, and May 1 and 4, 2001.

Our reviews of the Clinical Pharmacology & Biopharmaceutics, Pharmacology/Toxicology, and Clinical sections of your submissions are complete, and we have identified the following deficiencies:

Clinical Pharmacology & Biopharmaceutics

1. There is uncertainty as to the cross-reactivity of impurities in the drug product when using the RIA for detection of pegvisomant concentrations in serum. It is possible that some of these impurities are bioactive. You will need to purify these impurities and evaluate their cross-reactivity with the RIA as well as their bioactivity. Together, these procedures will contribute to the understanding of the active components of pegvisomant.
2. There are data that show an interaction between octreotide and cyclosporin which may be growth hormone mediated. Since pegvisomant can cause an apparent decrease in growth hormone by blocking receptors, you should conduct an *in vivo* drug interaction study to address any potential pharmacokinetic interaction between pegvisomant and cyclosporin.
3. There are no data submitted on the route of elimination of pegvisomant in humans. You need to provide data showing the route of elimination and/or metabolic pathways of pegvisomant. These data may be the basis for future recommendations of pharmacokinetic studies in special populations (e.g., hepatic and/or renal impairment).
4. To further understand the metabolic effects that pegvisomant may have on other drugs, you will need to conduct in vitro metabolism/drug interaction studies as per the guidance, "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro" (http://www.fda.gov/cder/guidance/clin3.pdf).

Pharmacology/Toxicology

1. A six-month non-rodent toxicity study with daily administration of the clinical formulation must be completed prior to approval. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25X human dose) is recommended.
2. The rabbit teratology study should be repeated with at least one dose high enough to produce signs of maternal toxicity in rabbits using the to-be-marketed drug product.
3. Please submit a protocol for a two-year rodent carcinogenicity study for review by the Executive Carcinogenicity Assessment Committee prior to initiation of the study. A carcinogenicity study must be conducted as a Phase 4 commitment.
4. A study monitoring renal function in acromegalic patients should be considered to assess the renal effects of chronic daily dosing of a pegylated compound.

Clinical

1. Establish a registry of acromegalic patients treated with pegvisomant in order to better monitor the rate of spontaneous reporting of liver test (LT) abnormalities during the initial marketing of pegvisomant.
2. Obtain additional immunogenicity data (including anti-pegvisomant antibodies*, anti-growth hormone (GH) antibodies and anti-vector protein antibodies) when the purity of the product to be marketed has improved to an acceptable level (as determined by the Division's Chemistry Reviewer).
   **Development of a validated assay for anti-pegvisomant antibodies which can be performed in the presence of therapeutic serum levels of pegvisomant should be considered.*
3. A three-armed trial comparing the efficacy of pegvisomant (e.g., percent reduction in IGF-I levels) without a loading dose, and after loading doses of 40 and 80 mg, should be considered.
4. Treat a larger number of acromegalics for much longer periods of time in order to demonstrate that the anti-acromegalic efficacy of pegvisomant does not wane after years of therapy.
5. Consider comparing the efficacy of pegvisomant and somatostatin analogue (SA) therapy (the primary medical therapy for acromegaly currently available) head to head.
6. Consider further exploring the utility of adding SA therapy to pegvisomant therapy in patients with clinically and biochemically resistant acromegaly with or without evidence of progressive growth of the underlying GH-secreting pituitary adenoma.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. Further, we have not yet completed labeling comments. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Margaret Simoneau
5/17/01 02:26:27 PM
Signing for Enid Galliers

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

9/27/01

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
98 San Jacinto Blvd., Suite 430
Austin, TX 78701

Dear Dr. Davis:

Please refer to your December 22, 2000, new drug application for Somavert (pegvisomant) Vials, 10, 15, 20 mg and our acknowledgment letter of January 24, 2001.

As we discussed by telephone on February 27, 2001, please note that the correct primary user fee goal date is June 26, 2001. We do apologize for any inconvenience.

If you have any questions, call me at (301) 827-6423.

Sincerely,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Crystal King
2/27/01 08:27:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-106

1/24/01

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
98 San Jacinto Blvd., Suite 430
Austin, TX 78701

Dear Dr. Davis:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Somavert (pegvisomant) Vials, 10, 15, 20 mg
Review Priority Classification:	Priority (P)
Date of Application:	December 22, 2000
Date of Receipt:	December 26, 2000
Our Reference Number:	NDA 21-106

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 24, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 24, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). However, this requirement does not apply to designated orphan indications. Therefore, you need not submit this information.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please me at (301) 827-6423.

Sincerely,

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Crystal King
1/24/01 10:53:39 AM

King

NDA 21-106

JAN 20 2000

Sensus Drug Development Corporation
Attention: Mike Bernstein, M.P.H.
Senior Director, Regulatory Affairs
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Dear Mr. Bernstein:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product:	pegvisomant subcutaneous injection
Date of Application:	December 16, 1999
Date of Receipt:	December 16, 1999
Our Reference Number:	NDA 21-106

We will review this early submission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all additional pre-submissions as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: CENTRAL DOCUMENT ROOM
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

If you have any questions, call me at (301) 827-6423.

Sincerely yours,

/S/

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-106
HFD-510/Div. Files
HFD-510/C.King
HFD-510/Reviewers and Team Leaders

DISTRICT OFFICE
HFD-820/DNDC Division Director

Drafted by: CKing/01.19.00
Initialed by: CKing/01.19.00
final: CKing/01.19.00
filename: mydoc/NDA/21106/ackroll#1011900

PRESUBMISSION UNDER ROLLING REVIEW PROGRAM ACKNOWLEDGEMENT (AC)

IND ——

DEC 7 1999

Sensus Drug Development Corporation
Attn: Mike Bernstein, M.P.H.
Senior Director, Regulatory Affairs
98 San Jacinto Boulevard
Austin, TX 78701

Dear Mr. Bernstein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for B2036-PEG, pegvisomant.

We also refer to our March 18, 1999, letter granting fast track designation for B2036-PEG for acromegaly and to your November 16, 1999, request for step-wise submission of sections of the New Drug Application (NDA) for this product.

We have reviewed your request and have concluded that the proposed plan for step-wise submission of sections of the NDA is acceptable.

If you pursue a clinical development program that does not support use of B2036-PEG for acromegaly, the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely yours,

/S/ 12-7-99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival IND
HFD-510/Division File
HFD-510/RPM
HFD-510/Team Leaders and Reviewers
HFD-094/DDMS-RMT

Drafted by: CKing/12.03.99
Initialed by: EGalliers/12.07.99
Final: CKing/12.07.99
filename: mydoc/NDA/21106/rollingOK

ROLLING REVIEW GRANTED (GR)

KING

IND —

MAR 18 1999

Sensus Drug Development Corporation
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Attention: Mike Bernstein, M.P.H.
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for B2036-PEG.

We also refer to your January 18, 1999, request for Fast Track Drug designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for Fast Track designation. Therefore, we are designating B2036-PEG for acromegaly as a Fast Track product.

We are granting Fast Track designation for the following reasons:

1. Acromegaly, almost always the consequence of a growth hormone (GH)-secreting pituitary adenoma, is a serious disease with significant morbidity and increased mortality. Persons with acromegaly frequently develop hypertension, diabetes, cardiovascular disease and generalized organomegaly among other morbidities. Untreated acromegalics and acromegalics with persistent disease despite therapy have a mortality rate approximately two to five times that of the normal population, as well as a five to ten year reduction in life expectancy. Biochemical cure following treatment results in mortality rates equivalent to that in matched controls; therefore, tight control is now considered to be a desired and required goal of therapy.

2. Current treatment options for acromegaly are inadequate in 30 to 40 percent of patients. Surgical cure is possible in only 30 to 40 percent of those able to be treated. The effects of radiation therapy are delayed and are frequently inadequate. Currently available drug therapies (somatostatin analogs and dopamine agonists) do not result in biochemical cure in a substantial number of acromegalics and have frequent adverse effects.

3. B2036-PEG, a GH receptor antagonist, is being developed by Sensus to increase the therapeutic options available to acromegalics. Unlike somatostatin analogues, it does not require the presence of functional somatostatin receptors in GH-secreting pituitary adenomas. Therefore, it is

believed that the drug could be effective in a larger percentage of acromegalics who have failed surgical therapy, including somatostatin analogue non-responders. Phase 2 trial results appear to support this hypothesis.

If you pursue a clinical development program that does not support use of B2036-PEG for acromegaly, the application will not be reviewed under the Fast Track program.

If you have any questions, contact Crystal King, Regulatory Project Manager, at (301) 827-6423.

Sincerely yours,

/S/ 3/18/97

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival IND
HFD-510 Division File
HFD-510 CKing/RPerlstein/SMalozowski/WBerlin/SMoore/RSteigerwalt
HFD-101/Carter

Drafted by: CKing 03.16.99
Initialed by: RPerlstein, SMalozowski, EGalliers 03.18.99
Final: CKing 03.18.99
filename: mydoc/INL FT 031699

FAST TRACK GRANTED (GR)

KING

IND

JAN 29 1999

Sensus Drug Development Corporation
San Jacinto Center
98 San Jacinto Boulevard
Suite 430
Austin, TX 787801

Attention: Mike Bernstein, M.P.H.
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

We have received your request for Fast Track designation submitted under section 506 of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

Name of Drug: B2036-PEG

Proposed Indication: To treat acromegaly

Date of Submission: January 18, 1999

Date of Receipt: January 19, 1999

Your request is under review and we will respond to you within 60 days of the above date of receipt.

If you have any questions, contact me at (301) 827-6423.

Sincerely yours,

/S/

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival IND
HFD-510/Division File
HFD-510/CKing
HFD-101/Carter

Drafted by: CKing/01.27.99
Initialed by: EGalliers
Final: CKing
filename: mydoc/ind/

FAST TRACK ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 24, 1997

Sensus Corporation
98 San Jacinto Blvd., Suite 430
Austin, Texas 78701

Attention: Robert J. Davis, Pharm. D.
Executive Vice President

Dear Dr. Davis:

Reference is made to your orphan drug application of April 3, 1997 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of Trovert™ (B2036-PEG) as an orphan drug (application 97-1050).

We have completed the review of this application and have determined that qualifies for orphan designation for the treatment of acromegaly. Please note that it is Trovert™ and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity.

Also please be advised that if Trovert™ were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of Trovert™ as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. Donald R. Haggerty at (301) 827-0986.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

08-29-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-106

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
San Jacinto Center
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Dear Dr. Davis:

Please refer to the meeting between representatives of your firm and FDA on July 18, 2001. The purpose of the meeting was to discuss two chemistry deficiencies listed in the Approvable Letter issued by the Agency on June 26, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301-827-6429.

Sincerely,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

08-03-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-106

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
San Jacinto Center
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Dear Dr. Davis:

Please refer to the meeting between representatives of your firm and FDA on July 18, 2001. The purpose of the meeting was to discuss two chemistry deficiencies listed in the Approvable Letter issued by the Agency on June 26, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6423.

Sincerely,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-106

Sensus Drug Development Corporation
Attention: Robert Davis, Pharm.D.
Executive Vice President
San Jacinto Center
98 San Jacinto Boulevard, Suite 430
Austin, TX 78701

Dear Dr. Davis:

Please refer to the meeting between representatives of your firm and FDA on July 12, 2001. The purpose of the meeting was to discuss pharmacology/toxicology deficiencies listed in the Approvable Letter issued by the Agency on June 26, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6423.

Sincerely yours,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Ed. Calamine

sensus

Fax

To:	Crystal King	Fax #: Phone:	301-443-9282 301-827-6423
From:	Nick Vrolijk	Fax #: Phone #:	919-490-0638 919-490-6728
Date:	14 September 2000	Pages:	4
Subject:	Stability protocol design		
cc:	Regulatory Files		

Crystal,

Attached please find a letter outlining the proposed experimental designs for stability studies we will be committing to in our NDA. We are in the initial stages of manufacturing drug substance that will be used for these protocols, so we would like to get input from our reviewers at their earliest convenience.

Thank you for your attention to this matter.

Sincerely,

Nick Vrolijk

14 September 2000

Steven Moore, Ph.D.
Chemistry Team Leader
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: IND ———
Recombinant Human Growth Hormone Antagonist

Dear Dr. Moore:

Sensus Drug Development Corporation is in the final stages of preparing Item 4 of our NDA submission for Pegvisomant. In the submission, we will be describing proposed stability studies for both drug substance and drug product that will be initiated in conjunction with our manufacturing process qualification or conformance runs. I would like your input on the experimental design for these protocols. Since we expect to begin the final stages of API manufacturing in approximately 1 month, I would also like to request a teleconference at your earliest convenience to discuss and resolve any issues you foresee regarding our proposed study designs.

Drug Substance Stability

Background

Pegvisomant Formulated Bulk Drug Substance is manufactured at 3 protein concentrations: 5.0, 7.5, and 10.0 mg/mL. The excipient concentrations are constant for all 3 formulations. The present storage condition for formulated bulk drug substance is -70°C.

Previous Stability Results

To date, 3 lots of formulated bulk drug substance have been put on stability (1 lot at 10.0 mg/mL and 2 lots at 5.0 mg/mL). The design for this earlier study is summarized as follows:

Storage Temperature	Time Points (months)
-70°C	0, 1, 3, 6, 9, 12
2-8°C	0, 1, 3, 6
25°C	0, 1, 2

Experimental Design

Sensus is interested in assessing -20°C storage for the formulated bulk drug substance. Therefore, the following design is proposed to assess this new storage temperature and to extend the storage time to 2 years.

Storage Temperature	Time Points (months)
-70°C	0, 3, 6, 9, 12, 18, 24
-20°C	0, 3, 6, 9, 12, 18, 24
2-8°C	0, 1, 3, 6

This proposed study will be performed with a total of 5 lots of formulated bulk drug substance. Three of these lots (one of each protein concentration) will represent drug substance from the 3 process qualification or conformance runs. The protein strengths will be bracketed as follows:

- 2 lots at 5.0 mg/mL
- 1 lot at 7.5 mg/mL
- 2 lots at 10.0 mg/mL

Based on results from our previous stability study, we believe that the stability of these 3 formulations (*i.e.* 3 protein concentrations) is comparable.

Drug Product Stability Protocol

Background

Pegvisomant Drug Product is manufactured at 3 strengths: 10, 15, and 20 U/vial. The excipient concentrations remain constant for all 3 formulations. The proposed storage temperature for Pegvisomant Drug Product will be 25°C.

Previous Stability Results

To date, 16 lots of Pegvisomant Drug Product have been put on stability. This represents every lot that has been manufactured, all at commercial scale. Initial studies were focused on 2-8°C as the storage temperature and 25°C was the accelerated condition. Interim analysis indicated that the drug product was stable at room temperature. Existing protocols were revised and new protocols were written to reflect this change and to incorporate ICH Guidelines. In the NDA, we will present data for 6 lots (3 lots at 10 U/vial, 3 lots at 20 U/vial) representing 24 months (3 lots), 18 months (2 lots), and 12 months (1 lot) storage at room temperature. In addition, we will present 12 months accelerated (40°C,) data on 3 lots of Drug Product.

Experimental Design

For this study, we are proposing to put 3 lots of Drug Product on stability, one of each product strength. These 3 lots will represent the 3 process qualification or conformance lots. The storage conditions and time points will be as follows:

Storage Temperature	Time Points (months)
25°C	0, 3, 6, 9, 12, 18, 24
40°C	0, 1, 3, 6

Based on results from our previous stability studies, we believe that the stability of these 3 product strengths is comparable, and that 1 lot of each strength is adequate for this study.

Thank you for your time and we look forward to speaking with you.

Sincerely,

/S/

Nicholas H. Vrolijk
Director Manufacturing Services

/S/

/S/

/S/